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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,830	VON DER MULBE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006 and 02 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-23 and 29-34* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-16 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 2/2/2007, in which claims 2, 3, 5 and 24-28 were canceled. Currently, claims 1, 4, 6-23 and 29-34 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant elected Group I with traverse in the reply filed on 7/1/2005.

Claims 17-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/1/2005.

Currently, claims 1, 4, 6-16 and 29-34 are under consideration.

Specification – Computer Program Listing

The description portion of this application contains a computer program listing consisting of more than three hundred (300) lines. In accordance with 37 CFR 1.96(c), a computer program listing of more than three hundred lines must be submitted as a computer program listing appendix on compact disc conforming to the standards set forth in 37 CFR 1.96(c)(2) and must be appropriately referenced in the specification (see 37 CFR 1.77(b)(5)). Accordingly, applicant

is required to cancel the computer program listing appearing in the specification on pages 30-67, file a computer program listing appendix on compact disc in compliance with 37 CFR 1.96(c) and insert an appropriate reference to the newly added computer program listing appendix on compact disc at the beginning of the specification. This objection was made in the Office action mailed 4/17/2006. Applicant has amended the specification to cancel the computer program listing and insert an appropriate reference to the newly added computer program listing appendix on CD. However, the CD could not be located.

Response to Arguments - Claim Objections

The objection of claim 25 is moot in view of Applicant's cancellation of the claim in the reply filed 2/2/2007

Claim Rejections - 35 USC § 112

Claims 1, 4, 6-16 and 29-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 4/17/2006 and has been rewritten to address the amendments to the claims in the reply filed 2/2/2007.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to pharmaceutical compositions comprising an mRNA that encodes a polypeptide that is biologically active or antigenic. Thus, the claims encompass mRNA compositions for therapeutic purposes or vaccines.

Claim 1 and claims that depend therefrom are drawn to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide that is biologically active or antigenic, wherein the modified mRNA has the following characteristics: (i) an increase in Guanine/Cytosine (G/C) content relative to that of wild type mRNA encoding the polypeptide, (ii) a maximum G/C content, (iii) a sequence that encodes a polypeptide with a sequence identical to the wild type polypeptide, and (iv) a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA. Dependent claims 4 and 6-10 further limit the structure of the modified mRNA of claim 1. Dependent claims further limit the polypeptide encoded by the modified mRNA to a growth factor, tumor antigen, viral antigen, bacterial antigen or protozoal antigen (claim 11), a secreted polypeptide that is a viral, bacterial or protozoal antigen (claim 12), a polyepitope of a growth factor, tumor antigen, viral antigen, bacterial antigen or protozoal antigen (claim 13), a polyepitope of a tumor antigen, viral antigen, bacterial antigen or protozoal antigen (claim 14), a cytokine (claim 15), or a tumor antigen (claim 29). Claim 16 further limits the pharmaceutical composition comprising the modified mRNA to one that also comprises at least one cytokine.

Claim 30 is drawn to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide that is biologically active or antigenic, wherein the

mRNA has the following characteristics: (i) maximum G/C content, and (ii) a sequence that encodes a polypeptide with a sequence identical to the wild type polypeptide.

Claim 31 and claims that depend therefrom are drawn to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide, and a pharmaceutically compatible carrier and/or vehicle, wherein said modified mRNA has the following characteristics: (i) increase in G/C content relative to the wild type mRNA, and (ii) a sequence encoding a tumor antigen. Claim 32 further limits the increase in G/C content to at least 15% relative to that of the wild type mRNA encoding the tumor antigen. Claim 33 further limits the modified mRNA of claim 31 to one that has at least one codon of a wild type sequence recognized by a rare cellular tRNA replaced with a codon recognized by an abundant cellular tRNA, which recognizes the same amino acid as the rare cellular tRNA. Claim 34 is drawn to the pharmaceutical composition of claim 31, wherein the modified mRNA comprises a maximum G/C content and a maximum number of codons recognized by abundant tRNAs.

The nature of the subject matter is complex, because the nucleic acid must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

Breadth of the claims: The claims are broad in that they encompass pharmaceutical compositions comprising at least one modified mRNA encoding any polypeptide that has biological activity or is antigenic. Thus, the claims encompass pharmaceutical compositions for the treatment of any disease or for the vaccination against any infection or cancer. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions the use of the modified mRNA for gene therapy and genetic vaccination for

prophylactic and/or therapeutic treatments. The specification broadly envisions increasing or maximizing the G/C content of the mRNA to increase stability of the message and increasing the number of codons that are recognized by abundant cellular tRNAs rather than rare tRNAs to increase the translation efficiency of the message. With regard to gene therapy, the specification envisions the treatment of diseases with a modified mRNA encoding dystrophin, cystic fibrosis conductance transmembrane regulator (CFTR), enzymes that are lacking in metabolic disorders such as phenylketonuria, galactosaemia, homocystinuria, adenosine deaminiase deficiency, enzymes that are involved in the synthesis of neurotransmitter, insulin, growth hormones, etc. The specification thus envisions the use of the modified mRNA for the treatment of inherited Mendelian disorders, including inborn errors of metabolism, and complex traits such as neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, diabetes, etc (e.g. paragraph [0050]). With regard to vaccination, the specification envisions the use of a modified mRNA for vaccination against virtually any infectious disease or cancer (e.g. paragraphs [0051]-[0052]).

While the specification and working examples teach how to make a modified mRNA that meets the structural characteristics of the claimed invention, the specification does not teach how to use the pharmaceutical compositions for any therapy. No working examples that demonstrate a therapeutic outcome are provided.

State and predictability of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J.

Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Regarding viral methods for gene delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

The area of the invention is unpredictable. As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The use of RNA for vaccinations is unpredictable in that the process depends upon cell-specific and tissue-specific efficient transfer of the nucleic acid (e.g. specification, paragraph [0009]). Furthermore, the success of nucleic acid vaccination is unpredictable with regard to obtaining a prophylactic or therapeutic effect (Dunham, S.P. Research in Veterinary Science,

Vol. 73, pages 9-16, 2002; e.g. pages 13-14). Dunham teaches that each vaccine in development must be optimized with regard to route and dose of inoculation for each target species due to the unpredictable nature of nucleic acid vaccines and the suboptimal delivery of the nucleic acid vaccine in many situations (e.g. page 13, right column, last paragraph; Table 1). In fact, the efficacy of genetic vaccines in many systems has not proven satisfactory, which has led some to conclude that genetic vaccines are not a viable alternative to conventional vaccines and may not be sufficiently immunogenic for the therapeutic vaccination of patients with infectious diseases or cancer in clinical trials (Lietner et al, Vol. 18, pages 765-777, 2000; e.g. Abstract, and page 766, right column).

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods commensurate in scope with the claims. With any modified mRNA one would have to determine how to deliver the given mRNA the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 4, 6-16 and 26-34 are not considered to be enabled by the instant specification.

Response to Amendment – Declaration of Dr. Ingmar Hoerr

The declaration under 37 CFR 1.132 filed 10/17/2006 is insufficient to overcome the rejection of claims 1, 4, 6-16 and 29-34 based upon insufficiency of disclosure under 35 U.S.C. 112, first paragraph, as set forth in the last Office action.

The showing is not commensurate in scope with the claims. The claims encompass pharmaceutical compositions that comprise a modified mRNA that encodes a biologically active peptide (i.e., for gene therapy). The claims broadly encompass a genus of pharmaceutical compositions that comprise a modified mRNA that encodes an antigen. Claims 1, 4, 6-10, 15, 16 and 30 read on any antigen. Claims 11-14 are drawn to or encompass any tumor antigens, any viral antigen, any bacterial antigen, and any protozoal antigen. Claims 29 and 31-34 are drawn to any tumor antigen. The claims are not drawn to any specific antigen from an infection or tumor.

The declaration demonstrates that a GC-enriched mRNA coding for ovalbumin was able to induce ovalbumin-specific IgG1-antibodies in mice. The induction of the immune response was able to reduce tumor size in mice that harbored syngenic tumor cells transfected with chicken ovalbumin antigen. The ovalbumin antigen is a foreign protein that was introduced into syngenic tumor cells. It is not a naturally occurring tumor antigen. The chicken ovalbumin antigen is an antigen that may fall within the broad class of antigens claimed, but is not an antigen isolated from a tumor, a viral antigen, a bacterial antigen or a protozoal antigen.

The declaration provides evidence that GC-enriched mRNA coding for luciferase resulted in increased expression in human PBMCs and in mice as compared to the wild type mRNA. Luciferase expression does not provide a measure of vaccine efficacy. The declaration asserts

that luciferase expression supports the use of the invention for gene therapy. The expression of luciferase in a mouse does not demonstrate any therapeutic effect. While, the GC-enriched mRNA may provide higher levels of gene expression, all of the problems recognized in the art (see pages 8-9 of the Office action mailed 4/17/2006) have not been addressed.

The declaration provides evidence that in vivo immunization of mice with influenza A matrix protein M1, GC-enriched mRNA results in the generation of cytotoxic T-lymphocyte response against Flu and lysis of target cells. This example provides evidence that a single viral antigen is effective at producing an immune response in mice.

The declaration provides evidence that GC-enriched mRNA coding for Influenza A induces IL-6 and TNFα in human PBMCs. This example provides evidence that the flu antigen induces an inflammatory reaction in human PBMCs.

The declaration provides evidence that compositions comprising wild type mRNA for multiple tumor antigens, in combination with a wild type mRNA for an influenza antigen was capable of reducing tumor burden in one human individual with renal cell carcinoma and a second human individual with melanoma. The instant claims are not drawn to wild type mRNA compositions. Furthermore, the claims do not require a combination of tumor and viral antigens. At page 4, paragraph 15, the declaration notes that viral antigens are used to increase the immune response against the tumor antigens, because viral antigens are very immunogenic and, since most people have had an infection with influenza, the immune system becomes stimulated very strongly. The wild type mRNA compositions comprise a GC-enriched mRNA coding for hepatitis B surface (HBS) antigen only as a marker for antibody induction, because the detection

of HBS antibodies is a standard procedure in the clinic (paragraph 15). The declaration does not provide evidence that the HBS antigen is an effective vaccine.

Upon comparing the steps, materials and conditions used in the experiments of the declaration with those disclosed in the application, it has been determined that the experiments of the declaration are not commensurate in scope with the guidance provided in the specification and the scope of the claims. Considering the evidence as a whole, the declaration is insufficient to overcome the rejection of claims 1, 4, 6-16 and 29-34 under 35 U.S.C. 112, first paragraph.

Response to Arguments - 35 USC § 112

With respect to the rejection of claims 1, 4, 6-16 and 29-34 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Applicant's arguments filed 2/2/2007 (copy of arguments provided on 10/17/2006) have been fully considered but they are not persuasive.

The response asserts that the declaration by Dr. Ingmar Hoerr, provided under 37 C.F.R. § 1.132, addresses the Examiner's concerns with regard to the unpredictability of using mRNA as a vaccine. This is not found persuasive for the reasons set forth above under the section titled *Response to Amendment – Declaration of Dr. Ingmar Hoerr.*

The response notes that modified mRNAs were shown to be more efficiently expressed than wild type mRNA both *in vitro* and *in vivo*. The response asserts that because the modified mRNAs are more efficiently expressed than wild type mRNA, the issues and state of predictability in the art should not be extended to the modified stabilized mRNA compositions of the present invention. However, expression does not necessarily predict the ability to vaccinate.

Other obstacles to vaccination are route of delivery and tissue-specific efficient transfer of the nucleic acid such that the expressed protein is sufficiently immunogenic for the particular species of organism (see page 9 of the Office action mailed 4/17/2006). These issues are not addressed by increasing the level of expression per mRNA molecule.

The response asserts that the declaration demonstrates a therapeutic outcome with immunization of mice with modified ovalbumin mRNA and with human patients immunized with hepatitis B surface (HBS) antigen. The ovalbumin mRNA does not fall within the specific classes of antigen claimed: tumor, viral, bacterial or protozoal. The ovalbumin mRNA encodes a chicken protein. With respect to the treatment of cancer in humans, the declaration demonstrates that a combination of many wild type mRNAs encoding tumor antigens and viral antigens was able to reduce tumor burden in two human patients. The HBS mRNA was the only modified mRNA in the composition and was used to measure titer, because a routine clinical assay was available. It is not clear that administration of the modified HBS mRNA alone would have a therapeutic effect.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments - 35 USC § 102

The rejection of claim 24 under 35 U.S.C. 102(b) as being anticipated by Chen et al (WO 99/20774) is moot in view of Applicant's cancellation of the claim in the reply filed 2/2/2007.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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